When will Mendelian randomization become relevant for clinical and public health practice?

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Obtaining reliable evidence regarding which factors cause disease or influence disease progression is clearly central to the development of scientific medicine. There have been many high-profile failures in this regard, which stretch from health-related behaviours (e.g. dietary components that observational epidemiology strongly suggested protected against chronic disease that failed when tested in large-scale randomised controlled trials), through vitamin supplement use and hormone replacement therapy, to a large number of drugs that failed at phase 3 trial stage[1 2].Observational epidemiological studies are prone to confounding, reverse causation (when the disease process influences the exposure, rather than *vice versa*) and a variety of other biases[1], and cellular through to whole-animal laboratory studies also lead to many erroneous conclusions being drawn. There are many strategies that need to be adopted to ameliorate this situation, with the over-arching philosophy being that only very rarely does any single source of evidence adequately establish the veracity of causal claims. Several methods should be applied to any question, each of which will have potential sources of bias, but the origins of, and predicted influence of, these biases should be unrelated to each other. With such "triangulation" of evidence, more reliable causal inference should be achieved[3].

A powerful component of this evidence base can be provided by the application of a methodology which incorporates the natural randomization inherent in the generation of genetic individuality – the process of Mendelian randomization[4 5]**.** The basic principle of Mendelian randomization (MR) is straight-forward; it is that genetic variation generates differences between individuals that influence health outcomes that are not subject to the confounding or reverse-causation bias that distort observational findings[4 5] . This process can be considered analogous to randomisation in a randomised controlled trial (RCT)[4], and there are now many examples of its application[6] . These range from proofs of principle (LDL cholesterol, blood pressure, obesity and smoking increase the risk of coronary heart disease, CHD), demonstration of factors unlikely to be causal (e.g C Reactive Protein in relation to CHD, diabetes and several cancers), dispelling claims of health protection (e.g. moderate alcohol intake is not beneficial with respect to CHD risk) and the prediction of findings from pharmacological RCTs of both success and failure[5 6 7].

MR studies have benefited from analytical methods adapted from "instrumental variables" approaches in econometrics, allowing estimation of effect sizes and their precision[5]. These require careful translation, as they can differ in magnitude from reliable estimates from other sources. For example, since genetic variants generally relate to life-time differences in the exposure (e.g, LDL cholesterol) they relate more strongly to disease outcome (e.g. CHD) than would be seen in an

observational study or a relatively short term (a few years) RCT of cholesterol reduction[4 7]. More strikingly, an exposure that influences disease risk at a critical period of the lifecourse – as has been suggested for vitamin D levels during the pre-adult stage in relation to multiple sclerosis risk – will be uncovered by a MR study (since the genetic variants influence vitamin D levels across life), but an intervention (or observational study) outside of that time period would not be expected to recapitulate this finding[8].

Early MR studies tended to use single genetic variants and focus on a specific risk factor-disease association within one study population. More recently the rapid growth in established genotype-phenotype associations coming from genome wide association studies (GWAS) has led to there being large numbers of genetic variants for many exposures and a large number of disease outcomes with available GWAS data. In this issue of *JAMA* a group that have made major contributions to applying MR in the cardiovascular drug target context[7] report an extensive MR analysis of whether – and if so how – abdominal obesity (indexed by waist-to-hip ratio) influences risk of CHD and type II diabetes[9].They conclude that over and above its association with body mass index (BMI), abdominal adiposity has an influence on the risk of both diseases, and that with respect to CHD, triglycerides account for much of the elevated risk.

Publically available GWAS data from consortia were utilised to estimate the effect of abdominal adiposity on disease outcomes, in what are known as two-sample MR analysis[5]. This approach has additional assumptions to single-sample studies[5], but has the very considerable advantage of allowing estimation of the causal effects of a very large array of potential exposures on many disease outcomes. A platform, MR-Base, is now available that facilitates rapid two-sample MR interrogation of a myriad of such exposure-outcome associations[10]. In addition to data from GWAS consortia Emdin and colleagues utilised data from UK Biobank, and replicated the estimated causal effects on CHD and type II diabetes, and demonstrated that blood pressure is influenced by abdominal adiposity whilst a large range of other outcomes are not[9].

Several violations of the assumptions required for reliable application of MR[4] are possible, and Emdin and colleagues are to be congratulated for attempting to evaluate these, using a series of approaches mostly detailed in the online-only supplement to the paper[9]. Genetic variants may have additional (pleiotropic) effects which are not mediated through the exposure – in this case abdominal adiposity – that they are being utilised as instruments for. The polygenic risk score was shown not to be associated with confounding factors that waist to hip ratio itself was related to in UK Biobank, and whilst there may of course be unmeasured confounders the lack of association with measured variables is reassuring. Sensitivity analyses with different inclusion criteria for genetic

variants generated similar findings and an exemplary additional series of tests were applied (although a regression-based approach to detect evidence of overall pleiotropy and yield a valid causal estimates with relaxed assumptions[11] was not utilised).

In public health terms it has proved difficult to reduce obesity levels through interventions, and the same may be true for abdominal adiposity. In this situation intervening on causal mediators can reduce disease risk without the underlying factor being changed, which appears to have occurred with respect to obesity, where treatment of hypertension, widespread cholesterol lowering and other preventative interventions have led to a reduction in cardiovascular mortality whilst obesity levels have risen in many countries[12]. Abdominal adiposity is shown to influence several such mediators in the current paper, and triglyceride demonstrated to be potentially important with respect to CHD risk. A formal MR mediation analysis could be applied which would more robustly quantify the contribution of potentially treatable intermediaries[13], and targeting such could have important public health benefit.

In terms of disease prevention the current resource of GWAS studies of particular diseases is appropriate, as MR studies based on these indicate causes that could be modified to reduce disease risk. However it is often stated that such GWAS can help identify targets for disease treatment. This is not necessarily the case, however, since in many cases factors that trigger disease will not be the same as those that influence its progression. For example, lung cancer case-control GWAS identified genetic variation related to smoking intensity as the top hit, confirming smoking as a cause of lung cancer. Once lung cancer has developed, though, smoking cessation is not an effective treatment. A recent GWAS of Crohn's disease prognosis found completely independent genetic predictors of disease progression to those that had been identified for disease onset, and the genetic correlation between onset and prognosis was negative[14]. This illustrates what may be a general phenomenon, and suggests that to inform identification of treatment targets, and to be able to perform MR studies of such, more genetic studies of disease progression and prognosis are required.

MR is slowly beginning to generate data of clear clinical and public health relevance. Attention to MR data might have helped avoid several very expensive late stage clinical trial failures[7] and might improve prediction of what RCTs will show[15 16] (Ference x 2). The conclusion from the first extended presentation of MR 15 years ago remains apposite, however: "it is probably fair to say that the method offers a more robust approach to understanding the effect of some modifiable exposures on health outcomes than does much conventional observational epidemiology. Where possible randomized controlled trials remain the final arbiter of the effects of interventions intended to influence health, however."[4]

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